



## Lipid profile and renal safety of tenofovir disoproxil fumarate-based anti-retroviral therapy in HIV-infected Chinese patients



Junyang Yang<sup>a,b,1</sup>, Jun Chen<sup>a,1</sup>, Yongjia Ji<sup>a</sup>, Qi Tang<sup>a</sup>, Renfang Zhang<sup>a</sup>, Li Liu<sup>a</sup>,  
Yinzhong Shen<sup>a</sup>, Jingna Xun<sup>a</sup>, Wei Song<sup>a</sup>, Yang Tang<sup>a</sup>, Zhenyan Wang<sup>a</sup>, Tangkai Qi<sup>a</sup>,  
Hongzhou Lu<sup>a,b,c,d,\*</sup>

<sup>a</sup> Department of Infectious and Immune Diseases, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China

<sup>b</sup> Wenzhou Medical University, Wenzhou, Zhejiang, China

<sup>c</sup> Department of Infectious Diseases, Huashan Hospital Affiliated to Fudan University, Shanghai, China

<sup>d</sup> Department of Internal Medicine, Shanghai Medical College, Fudan University, Shanghai, China

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### ABSTRACT

**Background:** Tenofovir disoproxil fumarate (TDF) is an important component of antiretroviral therapy (ART) that has been widely used. The aim of this study was to observe the long-term impact of TDF-based ART on lipid metabolism profiles and renal functions in Chinese patients.

**Methods:** 414 and 124 HIV-infected, ART-naïve patients who initiated TDF-based regimens and non-TDF regimens respectively were retrospectively included. Demographic characteristics and clinical information of each patient was collected. Changes of lipid profiles and renal function, as well as the risk factors of hyperlipidemia and renal dysfunction were analyzed.

**Results:** After 96 weeks of ART, HIV viral loads were undetectable in 97.34% (403/414) of patients exposed to TDF. The plasma total cholesterol (TCH) increased from  $3.97 \pm 0.83$  mmol/L to  $4.53 \pm 0.87$  mmol/L ( $P < 0.001$ ), which did not show a significant difference comparing with non-TDF exposed group. By contrast, the plasma triglyceride (TG) levels increased, but were still lower than that in the non-TDF exposed group ( $0.26 \pm 1.24$  vs.  $0.89 \pm 1.78$ ,  $P < 0.001$ ). The mean estimated glomerular filtration rate (eGFR) decreased from  $127.29 \pm 24.04$  ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> at baseline to  $118.84 \pm 22.74$  ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> ( $P < 0.001$ ) in the TDF exposed group, while it increased in the non-TDF exposed group. In the TDF group, high body mass index (BMI) (OR = 1.13,  $P = 0.01$ ), high baseline TG (OR = 2.33,  $P < 0.001$ ) and receiving protease inhibitors (PIs) (OR = 7.58,  $P < 0.001$ ) were associated with hypertriglyceridemia after ART, while high baseline TCH predicted hypercholesterolemia (OR = 3.58,  $P < 0.001$ ). MSM (OR = 0.22,  $P = 0.02$ ) and baseline eGFR (OR = 0.90,  $P < 0.001$ ) was associated with renal dysfunction after ART.

**Conclusions:** TDF-based regimens are of good therapeutic effect among Chinese people. These regimens showed a better plasma lipid profile but mild renal dysfunction as compared to non-TDF based regimens. Patients with high BMI, high baseline TG, high baseline TCH and low baseline eGFR should be closely monitored when using TDF-based ART.

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\* Corresponding author at: Department of Infectious and Immunology, Shanghai Public Health Clinical Center, Fudan University, No. 2901 Caolang Road, Shanghai, China.

E-mail addresses: [460981135@qq.com](mailto:460981135@qq.com) (J. Yang), [qtchenjun@163.com](mailto:qtchenjun@163.com) (J. Chen), [jiyongjia@hotmail.com](mailto:jiyongjia@hotmail.com) (Y. Ji), [itscandys@126.com](mailto:itscandys@126.com) (Q. Tang), [zrf\\_1113@163.com](mailto:zrf_1113@163.com) (R. Zhang), [liuli@shaphc.org](mailto:liuli@shaphc.org) (L. Liu), [027465@163.com](mailto:027465@163.com) (Y. Shen), [xunjingna@163.com](mailto:xunjingna@163.com) (J. Xun), [songwei@shaphc.org](mailto:songwei@shaphc.org) (W. Song), [tangyang@shaphc.org](mailto:tangyang@shaphc.org) (Y. Tang), [a1s2r@163.com](mailto:a1s2r@163.com) (Z. Wang), [qitangkai@shaphc.org](mailto:qitangkai@shaphc.org) (T. Qi), [luhongzhou@fudan.edu.cn](mailto:luhongzhou@fudan.edu.cn) (H. Lu).

<sup>1</sup> Junyang Yang and Jun Chen contributed equally to this work.

### Background

Anti-retroviral therapy (ART) effectively inhibits HIV replication in the human body and improves the immune function, as well as reducing the mortality of people living with HIV (PLWH), and prolonging their life expectancy (Cohen et al., 2011). However, ART drugs are also associated with some adverse effects, including dyslipidemia and lipodystrophy syndromes, liver damage, renal tubular damage,

hypersensitivity skin rashes and central nervous system symptoms (Lucas and Nelson, 2015).

Tenofovir disoproxil fumarate (TDF) is an important component of the first line ART regimens in adults, recommend by the World Health Organization (WHO) (WHO, 2019). Interestingly, some studies reported that TDF has a lipid-lowering property, which may decrease the risk of cardiovascular diseases (Shen et al., 2015; Fabbiani et al., 2011; Tungsiripat et al., 2010; Randell et al., 2010; Shaheen et al., 2017). In hypercholesterolemic HIV-1-infected individuals, TDF-based ART can decrease total cholesterol (TCH) (Moyle et al., 2015). PLWH receiving TDF have a low risk of hypercholesterolemia compared with patients taking non-TDF regimens (Greig and Deeks, 2016). However, whether TDF-based ART regimens are able to offset hyperlipidemia caused by HIV infection and other ART drugs, particularly in the real world, is still unclear. Meanwhile, a previous study had shown the incidence of renal dysfunction was much higher in TDF exposed patients (Jafari et al., 2014; Atta et al., 2008; Ojeh et al., 2018), with patients of older age and co-morbidities at higher risk.

At present, TDF containing regimens also are first line ART options in China. However, study on the safety of TDF in Chinese population is rare as TDF was not approved by the Chinese Food and Drug Administration until 2008. Herein, we investigated the long-term impact of TDF-based ART on lipid metabolism and renal function in Chinese patients in the real world.

## Methods

### Study population

In this retrospective cohort study, patients who initiated ART at Shanghai Public Health Clinical Center from October 2013 to August 2015 were enrolled. The inclusion criteria were a positive HIV test, and age older than 16 years. The ART regimens included TDF or Zidovudine (AZT) and Lamivudine (3TC) in combination with a third drug (Efavirenz [EFV], Nevirapine [NVP], lopinavir/ritonavir [LPV/r] or Raltegravir). The exclusion criteria were discontinuing ART within 96 weeks because of adherence, failure to follow up, opportunistic infection, as well as tumor. The study protocol was submitted and approved by the Shanghai Public Health Clinical Center Ethics Committee (Ethics approval number: 2016-S-044-01). The Ethics Committee authorized this study without written informed consent from participants because the study was retrospective in nature.

### Data collection

All patient information was collected from the chart and the Hospital Laboratory Retrieval System (HLRS). The information collected in this study included the patient's demographic characteristics (e.g., gender, age, height, weight, and route of HIV transmission), disease-relevant information (e.g., CD4 + T cell count, HIV RNA load, serum TCH, serum triglyceride [TG], and serum creatinine [Scr]) and ART regimens. The estimated glomerular filtration rate (eGFR) was calculated using the formula  $eGFR = \frac{1.73}{\text{BSA}^2} \times \text{Scr}^{-1.154} \times \text{Age}^{0.729} \times \text{Sex}^{0.762}$  (Ma et al., 2006). The demographic characteristics were collected at baseline, and disease-relevant information was collected at baseline, week 2, 4, 8, and 12 and every 12 weeks thereafter, until week 96.

Hypercholesterolemia and hypertriglyceridemia were defined as  $TCH > 5.2 \text{ mmol/L}$  and  $TG > 1.7 \text{ mmol/L}$ , respectively (Shen et al., 2015; Anon, 2002). Renal dysfunction was classified as mild ( $60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2} \leq eGFR < 90 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ), moderate ( $30 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2} \leq eGFR < 60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ), and severe

( $eGFR < 30 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) based on eGFR (Horberg et al., 2010).

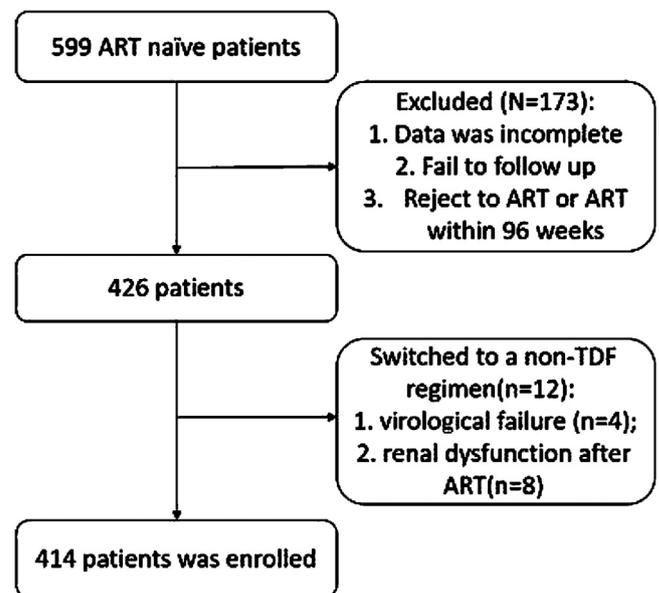
### Data analysis

All data were analyzed by IBM SPSS version 19.0 (IBM SPSS, Inc., Armonk, NY, USA). The figures were constructed using GraphPad Prism 6.0 software (GraphPad Software Inc., San Diego, CA, USA). Continuous variables are described as the mean and standard deviation (SD), while categorical variables are described by numbers and percentages. Paired-t-test or t-test was used to analyze continuous variables. Pearson's Chi-squared test and paired-t-tests were used for the univariate analysis. In addition, the logistic regression test was used to analyze the risk factors for renal dysfunction and dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) among TDF exposed patients. Factors with significant associations ( $P < 0.10$ ) in the univariate analysis were included in multivariate analysis. Statistical significance was defined by a conventional  $P$  value of 0.05 (two-tailed).

## Results

### Participant characteristics

The flow chart of this study is shown in Figure 1. A total of 426 individuals with TDF based ART regimens and 124 patients with non-TDF regimens were enrolled in this study. Twelve patients were excluded because of switching to non-TDF regimens. Of them, eGFR in eight patients declined to  $78.96 \pm 9.21 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , which were increased in 6/8 patients after switching to non-TDF regimens. However, it was only normalized in one patient. Those eight patients were still included in analyzing the risk factors of renal dysfunction. The other four patients switched to non-TDF regimens because of unsatisfied virological responses. The detailed baseline characteristics of the subjects were presented in Table 1.



**Figure 1.** Flow chart of this study. 12 patients switched to a non-TDF regimen and were excluded from this study. However, 8 patients of the 12 patients switched to a non-TDF regimen because of renal dysfunction after ART. Thus, they were also included in the analysis of renal function.

**Table 1**  
Baseline characteristics of the HIV-infected patients enrolled in this study.

Characteristic	TDF group (n = 414)	Non-TDF group (n = 124)	t or $\chi^2$	p
Age, years, mean (SD)	35.33 (11.09)	36.65(10.93)	1.16	0.25
Male, n (%)	400 (96.6%)	120(96.8)	0.01	0.93
CD4+T cell count (cells/ $\mu$ l), mean (SD)	347.78 (210.21)	337.63(214.02)	-0.46	0.64
CD4+/CD8+ rate, mean (SD)	0.37 (0.24)	0.39(0.32)	0.62	0.54
BMI <sup>a</sup> (kg/m <sup>2</sup> ), mean (SD)	22.06(2.91)	21.96(2.72)	-0.29	0.78
TCH <sup>b</sup> (mmol/L), mean (SD)	3.97 (0.79)	3.95(0.82)	-0.26	0.79
TG <sup>c</sup> (mmol/L), mean (SD)	1.59 (1.10)	1.56(0.99)	-0.29	0.77
eGFR <sup>d</sup> (ml·min <sup>-1</sup> ·1.73 m <sup>-2</sup> ), mean (SD)	127.29(24.04)	122.57(34.02)	-1.44	0.15
Route of HIV transmission, n (%)				
Blood transfusion	3 (0.72)	3 (2.42)	2.09	0.15
MSM <sup>e</sup>	288 (69.57)	83 (66.93)	0.31	0.58
Heterosexual	53 (12.80)	15 (12.10)	0.04	0.84
Unknown	70 (16.91)	23(18.55)	0.18	0.67
HBV <sup>f</sup> infection, n (%)	31 (7.49)	4(3.20)	3.55	0.06
HCV <sup>g</sup> infection, n (%)	10 (2.42)	0(0.00)	1.87	0.17
ART <sup>h</sup> regimens, n (%)				
2 NRTIs + 1 NNRTIs <sup>i</sup>	382 (92.26)	110(88.70)	1.55	0.21
2 NRTIs + 1 PIs <sup>j</sup>	31 (7.50)	14(11.30)	1.80	0.18
2 NRTIs + INIs <sup>k</sup>	1 (0.24)	0(0.00)	0.27	0.61
After ART				
CD4+T cell count (cells/ $\mu$ l), mean (SD)	432.69(192.80)	411.74(190.95)	-0.99	0.32
TCH (mmol/L), mean (SD)	4.53(0.87)	4.52(0.93)	-0.01	0.99
TG (mmol/L), mean (SD)	1.89(1.35)	2.42(2.00)	2.71	0.01
eGFR (ml·min <sup>-1</sup> ·1.73 m <sup>-2</sup> ), mean (SD)	118.84(22.74)	131.80(30.73)	4.23	<0.001

<sup>a</sup> BMI: body mass index = weight/height<sup>2</sup>.

<sup>b</sup> TCH: total cholesterol.

<sup>c</sup> TG: triglyceride.

<sup>d</sup> eGFR: estimated glomerular filtration rate<sup>e</sup>.

<sup>e</sup> MSM: homosexual men.

<sup>f</sup> HBV: hepatitis B virus.

<sup>g</sup> HCV: hepatitis C virus.

<sup>h</sup> ART: Anti-Retroviral Therapy.

<sup>i</sup> NNRTIs: non-nucleoside reverse transcriptase inhibitors, including 408 patients using Efavirenz and 13 patients using Nevirapine.

<sup>j</sup> PI: protease inhibitor, including lopinavir/ritonavir.

<sup>k</sup> INIs: integrase inhibitors, including Raltegravir.

### Virological and immunological responses

At the 96<sup>th</sup> week, HIV RNA level was below 50 copies/ml in 97.34% (403/414) patients. The CD4+T cell count sharply increased in the first 12 weeks of ART in both the TDF group (347.78 ± 210.21 vs. 421 ± 209.50,  $P < 0.001$ ) and the non-TDF group (337.63 ± 214.02 vs. 396.92 ± 201.18,  $P = 0.03$ ) (Figure 2.a.). After 96 weeks of ART, the two groups showed no significant difference in CD4+T cell count (432.69 ± 192.80 vs. 411.74 ± 190.95,  $P = 0.32$ ).

### Changes in serum lipids and renal function

In the TDF group, plasma TCH levels rose from 3.97 ± 0.83 mmol/L at baseline to 4.53 ± 0.87 mmol/L at week 96 ( $P < 0.001$ , Figure 2.b.), additionally the prevalence of hypercholesteremia increased from 6.5% at baseline to 19.3% at week 96 ( $P < 0.001$ ). There was no difference in TCH level changes between the TDF group and the non-TDF group. For the TDF group, TG levels increased from 1.59 ± 1.10 mmol/L at baseline to 1.81 ± 1.36 mmol/L after 4 weeks of ART ( $P < 0.001$ ). It remained relatively stable from week 4 to week 96 ( $P = 0.12$ ). The prevalence of hypertriglyceridemia increased from 29.7%, and 43.2% after 96 weeks of ART ( $P < 0.001$ ). Similar changes could be observed in the non-TDF group, but it also showed a higher increase in the first 4 weeks after ART (1.56 ± 0.99 vs. 2.29 ± 1.60,  $P < 0.001$ ). Besides, after 96 weeks of ART, patients with non-TDF regimens showed higher plasma TG level changes than TDF regimens (0.89 ± 1.78 vs. 0.26 ± 1.24,  $P = 0.01$ ).

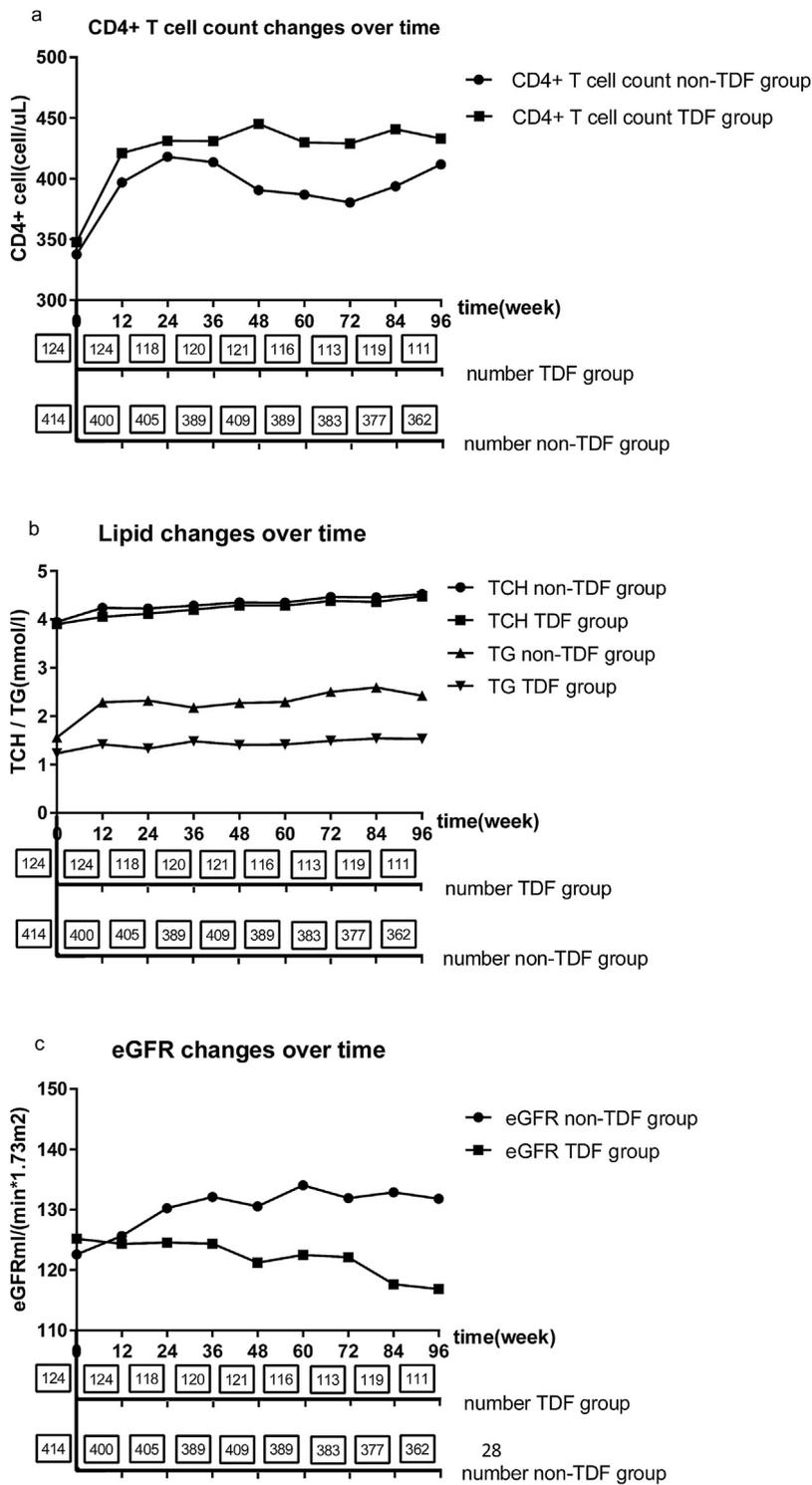
None of age, baseline CD4+T cell count, baseline CD4+/CD8+ rate, baseline eGFR, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection or homosexuality were associated with

hypercholesteremia or hypertriglyceridemia. High baseline BMI was associated with hypercholesteremia (OR = 1.19,  $P < 0.001$ ) in the univariate analysis but not in the multivariate analysis (OR = 1.13,  $P = 0.22$ ). However, patients with high baseline TCH (OR = 3.58,  $P < 0.001$ ) were more likely to develop hypercholesteremia (Table 2). In the multivariate analysis, high BMI (OR = 1.13,  $P = 0.01$ ), high baseline TG (OR = 2.33,  $P < 0.001$ ), and taking PIs (OR = 7.58,  $P < 0.001$ ) were associated with hypertriglyceridemia (Table 3).

After ART, eGFR in the TDF group declined from 122.89 ± 23.49 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> at baseline to 114.36 ± 21.43 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> at week 96. By contrast, the non-TDF group showed increased eGFR (122.57 ± 34.02 vs. 131.80 ± 30.73,  $P < 0.001$ , Figure 2.c.). No patient experienced acute kidney injury. After 96 weeks of ART, 38 (9.00%) patients, including 8 patients who had switched to non-TDF regimens, had mild renal dysfunction. MSM (OR = 0.22,  $P = 0.02$ ), patients with unknown transmission route of HIV (OR = 0.04,  $P = 0.02$ ), and those with high baseline eGFR (OR = 0.90,  $P < 0.001$ ) were not prone to renal dysfunction in both the univariate and multivariate analyses (Table 4). High BMI (OR = 1.19,  $P = 0.05$ ), older age (OR = 1.07,  $P < 0.001$ ) and HBV infection (OR = 2.54  $P = 0.06$ ) were also associated with renal dysfunction in the univariate analysis, but significance was lost in multivariate analysis.

### Discussion

TDF is still one of the backbone drugs of ART recommended by many countries. Previous studies have reported that ART with TDF can reduce the viral load of HIV in a short time, and exhibits an excellent therapeutic effect in PLWH (Wu et al., 2016). After 96 weeks of ART, most PLWH showed a well-controlled HIV viral load



**Figure 2.** Disease-relevant information changes over time in both TDF group and non-TDF group. (a) Mean CD4 + T cell count changes over 96 weeks of ART. (b) Mean TCH and TG changes over 96 weeks of ART. (c) Mean eGFR changes over 96 weeks of ART.

in this study. TDF-based ART can effectively restore the immune function of PLWH as reflected by the rapid increase in CD4 + T cell count in the first 12 weeks of ART and the slow increase in CD4 + T cell count afterwards. These results also have been supported by other studies (Wu et al., 2016; Gazzard et al., 2014; Zhou et al., 2017; Amiel et al., 2014). Compared with other regimens, TDF-based regimens showed no difference in the gain of CD4 + T cell count (Hemkens et al., 2015).

Many studies have demonstrated that ART can lead to a significantly increased prevalence of dyslipidemia (Wu et al., 2016; Zhou et al., 2017; Huang et al., 2015a; Molina et al., 2008; Ortiz et al., 2008), and HIV itself could result in dyslipidemia (Shen et al., 2015). The prevalence of hypercholesterolemia and hypertriglyceridemia in ART-naïve HIV-infected patients were similar to previous reports from China (Shen et al., 2015) and Africa (Armstrong et al., 2011). After 96 weeks of TDF-based ART, the prevalence of

**Table 2**  
Risk factors associated with hypercholesteremia in patient receiving TDF-based ART regimen.

Variable	Hypercholesteremia (n = 80)	Non-hypercholesteremia (n = 334)	Missing value	Univariate analysis		Multivariate analysis	
				p Value	OR (95% CI)	p Value	OR (95% CI)
Age (year), mean (SD)	37.46 (12.01)	34.81 (10.81)	0	0.06	1.02 (1.00–1.04)	0.97	1.00 (0.97–1.03)
Male, n (%)	78 (97.50)	322 (96.40)	0	0.63	0.68 (0.15–3.13)	–	–
BMI <sup>a</sup> (kg/m <sup>2</sup> ), mean (SD)	23.33 (2.90)	21.79 (2.87)	45	<0.001	1.19 (1.09–1.30)	0.22	1.13 (1.02–1.25)
Baseline CD4 + T cell count (cells/mm <sup>3</sup> ), mean (SD)	369.64 (201.31)	342.58 (212.26)	39	0.33	1.00 (0.99–1.01)	–	–
Baseline CD4+/ D8+ rate, mean (SD)	0.35 (0.20)	0.37 (0.26)	41	0.66	0.78 (0.27–2.31)	–	–
Baseline TCH (mmol/L), mean (SD)	4.62 (0.85)	3.81 (0.75)	6	<0.001	3.46 (2.42–4.95)	<0.001	3.58 (2.37–5.40)
Baseline TG (mmol/L), mean (SD)	1.83 (1.18)	1.54 (1.08)	6	0.04	1.23 (1.01–1.51)	0.87	0.98 (0.77–1.25)
Baseline eGFR (ml·min <sup>-1</sup> ·1.73 m <sup>-2</sup> ), mean (SD)	120.62 (21.72)	123.43 (23.89)	6	0.34	1.00 (0.99–1.01)	–	–
HBV infection, n (%)	5 (6.25)	26 (7.78)	67	0.61	0.77 (0.29–2.09)	–	–
HCV infection, n (%)	2 (2.50)	8 (2.40)	98	0.91	1.092 (0.23–5.28)	–	–
Taking PIs, n (%)	6 (7.50)	25 (7.49)	0	1.00	1.02 (0.40–2.53)	–	–
MSM, n (%)	54 (67.50)	234 (70.06)	70	0.73	0.88 (0.43–1.82)	–	–

BMI: Body Mass Index, TCH: total cholesterol, TG: triglyceride, eGFR: estimated glomerular filtration rate, HBV: hepatitis B virus, HCV: hepatitis B virus, PIs: proteinase inhibitors, MSM: homosexual men.

**Table 3**  
Risk factors associated with hypertriglyceridemia in patient receiving TDF-based ART regimen.

Variable	Hypertriglyceridemia (n = 179)	Non-hypertriglyceridemia (n = 235)	Missing value	Univariate analysis		Multivariate analysis	
				p Value	OR (95% CI)	p Value	OR (95% CI)
Age (years), mean (SD)	36.75 (11.08)	34.24 (11.00)	0	0.02	1.02 (1.00–1.04)	0.93	1.00 (0.98–1.03)
Male, n (%)	174 (97.21)	226 (96.17)	0	0.56	0.72 (0.24–2.19)	–	–
BMI (kg/m <sup>2</sup> ), mean (SD)	22.98 (3.03)	21.44 (2.69)	45	<0.001	1.21 (1.12–1.31)	0.01	1.13 (1.03–1.24)
Baseline CD4 + T cell count (cells/mm <sup>3</sup> ), mean (SD)	349.02 (208.94)	346.89 (211.60)	39	0.92	1.00 (1.00–1.00)	–	–
CD4+/CD8+ rate, mean (SD)	0.35 (0.23)	0.38 (0.26)	41	0.26	0.61 (0.26–1.44)	–	–
Baseline TCH (mmol/L), mean (SD)	4.00 (0.81)	3.9 (0.85)	6	0.42	1.10 (0.87–1.40)	–	–
Baseline TG (mmol/L), mean (SD)	2.01 (1.33)	1.27 (0.75)	6	<0.001	2.17 (1.68–2.80)	<0.001	2.33 (1.72–3.15)
Baseline eGFR (ml·min <sup>-1</sup> ·1.73 m <sup>-2</sup> ), mean (SD)	119.61 (23.76)	125.38 (23.03)	6	0.014	0.99 (0.98–1.00)	0.08	0.99 (0.98–1.01)
Hepatitis B infection, n (%)	7 (3.91)	24 (10.21)	67	0.01	0.35 (0.15–0.83)	0.20	0.80 (0.58–1.12)
Hepatitis C infection, n (%)	4 (2.23)	6 (2.55)	98	0.82	0.87 (0.24–3.14)	–	–
PIs, n (%)	21 (11.73)	10 (4.26)	0	0.004	2.99 (1.37–6.52)	<0.001	7.58 (2.79–20.63)
MSM, n (%)	118 (65.92)	170 (72.34)	70	0.40	0.78 (0.43–1.40)	–	–

BMI: Body Mass Index, TCH: total cholesterol, TG: triglyceride, eGFR: estimated glomerular filtration rate, HBV: hepatitis B virus, HCV: hepatitis B virus, PIs: proteinase inhibitors, MSM: homosexual men.

hypercholesteremia and hypertriglyceridemia increased, but were lower than that in the non-TDF regimens group.

Different ART regimens appear to promote different alterations in lipid metabolism (Souza et al., 2013). Some research has shown that TDF has a lipid-lowering property (Fabbiani et al., 2011; Tungsiripat et al., 2010; Behrens et al., 2012). Crane has claimed

that TDF-contained regimens were associated with lower lipid levels than other nucleoside reverse transcriptase inhibitors (NRTIs) -based regimens (Crane et al., 2011). Using TDF instead of other NRTIs can improve the lipid profile of patients with dyslipidemia (Libre et al., 2006). Though an obviously elevated lipid level was observed in this study, the degree to which plasma

**Table 4**  
Risk factors associated with renal dysfunction in patient receiving TDF-based ART regimen.

Variable	Renal dysfunction (n = 38)	Non-renal dysfunction (n = 384)	Missing value	Univariate analysis		Multivariate analysis	
				P value	OR (95% CI)	P value	OR (95% CI)
Age (years), mean (SD)	44.26 (12.17)	34.46 (10.65)	0	<0.001	1.07 (1.04–1.10)	0.08	1.04 (0.99–1.09)
Male, n (%)	35 (92.1)	373 (97.1)	0	0.12	2.90 (0.06–1.40)		
BMI (kg/m <sup>2</sup> ), mean (SD)	23.58 (2.39)	21.95 (2.92)	48	0.05	1.19 (1.05–1.34)	0.20	1.13 (0.94–1.36)
Baseline CD4+T cell count (cells/mm <sup>3</sup> ), mean (SD)	395.23 (304.40)	336.89 (200.23)	39	0.13	1.00 (1.00–1.00)		
CD4+/CD8+ rate, mean (SD)	0.40 (0.28)	0.36 (0.25)	49	0.36	1.80 (0.52–6.30)		
Baseline TCH (mmol/L), mean (SD)	4.11 (0.97)	3.94 (0.83)	14	0.22	1.27 (0.87–1.86)		
Baseline TG (mmol/L), mean (SD)	1.46 (0.97)	1.61 (1.11)	14	0.42	0.87 (0.61–1.23)		
Baseline eGFR (ml·min <sup>-1</sup> ·1.73 m <sup>-2</sup> ), mean (SD)	96.90 (20.17)	130.72 (23.10)	14	<0.001	0.91 (0.88–0.93)	<0.001	0.90 (0.87–0.94)
Hepatitis B infection, n (%)	6 (15.8)	28 (7.3)	67	0.06	2.54 (0.96–6.70)	0.82	1.21 (0.24–6.00)
Hepatitis C infection, n (%)	1 (2.6)	9 (2.3)	99	0.91	1.13 (0.14–9.26)		
PIs, n (%)	3 (7.9)	34 (8.9)	0	0.84	0.88 (0.26–3.02)		
MSM, n (%)	18 (47.4)	275 (71.6)	74	0.06	0.32 (0.15–0.72)		
Route of HIV transmission (vs. Heterosexual)							
MSM, n (%)	18 (47.37)	275 (71.61)	0	0.01	0.34 (0.14–0.79)	0.02	0.22 (0.06–0.76)
Others or unknown, n (%)	11 (29.95)	63 (16.41)	0	0.82	0.89 (0.34–2.33)	0.02	0.04 (0.00–0.59)

BMI: Body Mass Index, TCH: total cholesterol, TG: triglyceride, eGFR: estimated glomerular filtration rate, HBV: hepatitis B virus, HCV: hepatitis C virus, PIs: protease inhibitors, MSM: homosexual men.

TG rises among TDF exposed patients was lower than non-TDF exposed patients. However, TDF cannot completely normalize elevated TG caused by other ART or HIV infection drugs. Our study revealed that high BMI, high baseline TG and taking PIs were risk factors for hypertriglyceridemia, which is consistent with other research (Sun et al., 2015). Therefore, patients with these factors require close monitoring and further intervention after ART initiation.

Long-term TDF administration is likely to induce continuous renal function declines, albuminuria and chronic renal diseases (Horberg et al., 2010). In our study, eGFR declined in TDF exposed patients, while it increased in non-TDF exposed patients. TDF-related renal dysfunction has been reported more frequently in Asian countries than in Western countries (Gervasoni et al., 1999; Lichtenstein et al., 2001; Noor et al., 2002). Two Chinese cohorts showed average annual decreases in eGFR of 2.7 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> and 3.5 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> in TDF-exposed patients, respectively (Huang et al., 2015b; Cao et al., 2013). However, a relatively faster decrease (4.2 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> annually) in eGFR was observed in our study. Declines in eGFR induced by TDF increased over time (Nishijima et al., 2014), which may influence the prevalence of renal dysfunction at different time points after initial ART. During 96 weeks of ART, 9.0% patients presented with mild renal dysfunction, which is much higher than the rates previously reported in Chinese populations (4.2%–6.3%) (Tanuma et al., 2016; Kyaw et al., 2015). This difference may be attributed to different definitions of renal dysfunction (a 25% decline in creatinine clearance from baseline and an eGFR < 60 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>) in other studies. When it comes to the same definition, 52.2% of patients had renal dysfunction in Africa after 4–5 years of ART (Stohr et al., 2011). This is

remarkably higher than the corresponding result in our study. The reasons for this difference may be the prevalence of renal dysfunction increasing over time, and black people are more likely to develop renal dysfunction (Martins et al., 2002).

In this study, the incidence of renal dysfunction was not impacted by gender, age, BMI, HBV infection or HCV infection, as well as CD4+T cell count. Therefore, Chinese HIV patients with these concerns could still receive TDF-based therapy. Several studies had claimed that PLWH exposed to TDF and LPV/r were strongly associated with chronic kidney disease (Mizushima et al., 2018; Mwafongo et al., 2014). A similar result was observed in our study in univariate analysis, but it lost correlation in multivariate analysis. Additionally, patients with low baseline eGFR should avoid TDF or be closely monitored after initiating TDF-based regimens. Unexpectedly, MSM and the patients with unknown transmission route exposed to TDF were more unlikely to have renal dysfunction occur as compared with heterosexual counterparts in this study. Other studies also observed that transmission route was associated with renal dysfunction (Kim et al., 2017; Cheung et al., 2017). However, the underlying mechanism was still unknown. We also do not know why MSM patients present with less frequency of renal dysfunction. Larger studies are needed to verify this result.

There are several limitations in our study. First, in our retrospective design, some information is missing, including hypertension, diabetes and concomitant medications as well as lab tests, including very low-density lipoprotein, low-density lipoprotein and high-density lipoprotein levels. However, the prevalence of hypertension and diabetes are relatively low in young Chinese populations (13.0% and 3.2%, respectively) (Gao et al., 2013; Yang et al., 2010), which would not significantly impact

our results. Second, most patients were middle aged men from the Han population. Thus, our results could not extend to other populations in China.

## Conclusions

Triple anti-HIV therapy with TDF as the backbone is of good therapeutic effect among Chinese PLWH. These regimens showed better plasma lipid profile but mild renal dysfunction as compared to non-TDF based regimens. Patients with high BMI, high baseline TG, high baseline TCH and low baseline eGFR should be closely monitored when using TDF-based ART.

## Conflict of interest

No conflicts of interest have been reported.

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## Ethical approval

The study protocol was submitted and approved by the Shanghai Public Health Clinical Center Ethics Committee (Ethics approval number: 2016-S-044-01). The Ethics Committee authorized this study without written informed consent from participants because the study was retrospective natural.

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## References

Amiel C, Schneider V, Guessant S, Hamidi M, Kherallah K, Lebrette MG, et al. Initiation of rilpivirine, tenofovir and emtricitabine (RPV/TDF/FTC) regimen in 363 patients with virological vigilance assessment in 'real life'. *J Antimicrob Chemother* 2014;69:3335–9.

Anon. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143–421.

Armstrong C, Liu E, Okuma J, Spiegelman D, Guerino C, Njelekela M, et al. Dyslipidemia in an HIV-positive antiretroviral treatment-naïve population in Dar es Salaam, Tanzania. *J Acquir Immune Defic Syndr* 2011;57:141–5.

Atta MG, Deray G, Lucas GM. Antiretroviral nephrotoxicities. *Semin Nephrol* 2008;28:563–75.

Behrens G, Maserati R, Rieger A, Domingo P, Abel F, Wang H, et al. Switching to tenofovir/emtricitabine from abacavir/lamivudine in HIV-infected adults with raised cholesterol: effect on lipid profiles. *Antiviral Ther* 2012;17:1011–20.

Cao Y, Han Y, Xie J, Cui Q, Zhang L, Li Y, et al. Impact of a tenofovir disoproxil fumarate plus ritonavir-boosted protease inhibitor-based regimen on renal function in HIV-infected individuals: a prospective, multicenter study. *BMC Infect Dis* 2013;13:301.

Cheung J, Pühr R, Petoumenos K, Cooper DA, Woolley I, Gunathilake M, et al. Chronic kidney disease in Australian HIV-infected patients: analysis of the Australian HIV Observational Database. *Nephrology (Carlton)* 2017;.

Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;365:493–505.

Crane HM, Grunfeld C, Willig JH, Mugavero MJ, Van Rompaey S, Moore R, et al. Impact of NRTIs on lipid levels among a large HIV-infected cohort initiating antiretroviral therapy in clinical care. *AIDS* 2011;25:185–95.

Fabbiani M, Bracciale L, Doino M, Sidella L, Farina S, Di Cristo V, et al. Lipid-lowering effect of tenofovir in HIV-infected patients. *J Antimicrob Chemother* 2011;66:682–3.

Gao Y, Chen G, Tian H, Lin L, Lu J, Weng J, et al. Prevalence of hypertension in china: a cross-sectional study. *PLoS One* 2013;8:e65938.

Gazzard B, Girard PM, Di Perri G, Gallant J, Towner W, Rogatto F, et al. Long-term efficacy and safety of E/C/F/TDF vs EFV/FTC/TDF and ATV+RTV+FTC/TDF in HIV-1-infected treatment-naïve subjects <math>\geq 50</math> years. *J Int AIDS Soc* 2014;17:19767.

Gervasoni C, Ridolfo AL, Trifiro G, Santambrogio S, Norbiato G, Musicco M, et al. Redistribution of body fat in HIV-infected women undergoing combined antiretroviral therapy. *AIDS* 1999;13:465–71.

Greig SL, Deeks ED. Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide: a review in HIV-1 infection. *Drugs* 2016;76:957–68.

Hemkens LG, Ewald H, Santini-Oliveira M, Buhler JE, Vuichard D, Schandelmaier S, et al. Comparative effectiveness of tenofovir in treatment-naïve HIV-infected patients: systematic review and meta-analysis. *HIV Clin Trials* 2015;16:178–89.

Horberg M, Tang B, Towner W, Silverberg M, Bersoff-Matcha S, Hurley L, et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naïve patients. *J Acquir Immune Defic Syndr* 2010;53:62–9.

Huang X, Xu Y, Yang Q, Chen J, Zhang T, Li Z, et al. Efficacy and biological safety of lopinavir/ritonavir based anti-retroviral therapy in HIV-1-infected patients: a meta-analysis of randomized controlled trials. *Sci Rep* 2015a;5:8528.

Huang YS, Chan CK, Tsai MS, Lee KY, Lin SW, Chang SY, et al. Kidney dysfunction associated with tenofovir exposure in human immunodeficiency virus-1-infected Taiwanese patients. *J Microbiol Immunol Infect* 2015b;50:595–603.

Jafari A, Khalili H, Dashti-Khavidaki S. Tenofovir-induced nephrotoxicity: incidence, mechanism, risk factors, prognosis and proposed agents for prevention. *Eur J Clin Pharmacol* 2014;70:1029–40.

Kim EJ, Ahn JY, Kim YJ, Wie SH, Park DW, Song JY, et al. The prevalence and risk factors of renal insufficiency among Korean HIV-infected patients: the Korea HIV/AIDS cohort study. *Infect Chemother* 2017;49:194–204.

Kyaw NT, Harries AD, Chinnakali P, Antierens A, Soe KP, Woodman M, et al. Low incidence of renal dysfunction among HIV-infected patients on a tenofovir-based first line antiretroviral treatment regimen in Myanmar. *PLoS One* 2015;10:e0135188.

Lichtenstein KA, Ward DJ, Moorman AC, Delaney KM, Young B, Palella FJ, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS* 2001;15:1389–98.

Llibre JM, Domingo P, Palacios R, Santos J, Perez-Elias MJ, Sanchez-de la Rosa R, et al. Sustained improvement of dyslipidaemia in HAART-treated patients replacing stavudine with tenofovir. *AIDS* 2006;20:1407–14.

Lucas S, Nelson AM. HIV and the spectrum of human disease. *J Pathol* 2015;235:229–41.

Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006;17:2937–44.

Martins D, Tareen N, Norris KC. The epidemiology of end-stage renal disease among African Americans. *Am J Med Sci* 2002;323:65–71.

Mwafongo A, Nkanaunena K, Zheng Y, Hogg E, Samaneka W, Mulenga L, et al. Tenofovir disoproxil fumarate co-administered with lopinavir/ritonavir is strongly associated with tubular damage and chronic kidney disease. *J Infect Chemother* 2018;24:549–54.

Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* 2008;372:646–55.

Moyle GJ, Orkin C, Fisher M, Dhar J, Anderson J, Wilkins E, et al. A randomized comparative trial of continued abacavir/lamivudine plus efavirenz or replacement with efavirenz/emtricitabine/tenofovir DF in hypercholesterolemic HIV-1 infected individuals. *PLoS One* 2015;10:e0116297.

Mwafongo A, Nkanaunena K, Zheng Y, et al. Renal events among women treated with tenofovir/emtricitabine in combination with either lopinavir/ritonavir or nevirapine. *AIDS* 2014;28:1135–42.

Nishijima T, Kawasaki Y, Tanaka N, Mizushima D, Aoki T, Watanabe K, et al. Long-term exposure to tenofovir continuously decrease renal function in HIV-1-infected patients with low body weight: results from 10 years of follow-up. *AIDS* 2014;28:1903–10.

Noor MA, Seneviratne T, Aweeka FT, Lo JC, Schwarz JM, Mulligan K, et al. Indinavir acutely inhibits insulin-stimulated glucose disposal in humans: a randomized, placebo-controlled study. *AIDS* 2002;16:F1–8.

Ojeh BV, Abah IO, Ugoagwu P, et al. Incidence and predictors of tenofovir disoproxil fumarate-induced renal impairment in HIV infected Nigerian patients. *Germes* 2018;8:67–76.

Ortiz R, Dejesus E, Khanlou H, Voronin E, van Lunzen J, Andrade-Villanueva J, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1-infected patients at week 48. *AIDS* 2008;22:1389–97.

Randell PA, Jackson AG, Zhong L, et al. The effect of tenofovir disoproxil fumarate on whole-body insulin sensitivity, lipids and adipokines in healthy volunteers. *Antiviral Ther* 2010;15:227–33.

Shaheen AA, AlMattoq M, Yazdanfar S, Burak KW, Swain MG, Congly SE, et al. Tenofovir disoproxil fumarate significantly decreases serum lipoprotein levels compared with entecavir nucleos(t)ide analogue therapy in chronic hepatitis B carriers. *Aliment Pharmacol Ther* 2017;46:599–604.

- Shen Y, Wang J, Wang Z, Qi T, Song W, Tang Y, et al. Prevalence of dyslipidemia among antiretroviral-naive HIV-infected individuals in China. *Medicine* 2015;94:e2201.
- Souza SJ, Luzia LA, Santos SS, et al. Lipid profile of HIV-infected patients in relation to antiretroviral therapy: a review. *Rev Assoc Med Bras* 2013;59:186–98.
- Stohr W, Reid A, Walker AS, et al. Glomerular dysfunction and associated risk factors over 4–5 years following antiretroviral therapy initiation in Africa. *Antiviral Ther* 2011;16:1011–20.
- Sun D, Wu Y, Yuan Y, et al. Is the atherosclerotic process accentuated under conditions of HIV infection, antiretroviral therapy, and protease inhibitor exposure? Meta-analysis of the markers of arterial structure and function. *Atherosclerosis* 2015;242:109–16.
- Tanuma J, Jiamsakul A, Makane A, Avihingsanon A, Ng OT, Kiertiburanakul S, et al. Renal dysfunction during tenofovir use in a regional cohort of HIV-infected individuals in the Asia-Pacific. *PLoS One* 2016;11:e0161562.
- Tungsiripat M, Kitch D, Glesby MJ, Gupta SK, Mellors JW, Moran L, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. *AIDS* 2010;24:1781–4.
- WHO. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV Interim guidance. World Health Organization; 2019. . . [Accessed 13 January 2019] <https://www.who.int/hiv/pub/guidelines/ARV2018update/en/>.
- Wu YS, Zhang WW, Ling XM, Yang L, Huang SB, Wang XC, et al. Efficacy and safety of tenofovir and lamivudine in combination with efavirenz in patients co-infected with human immunodeficiency virus and hepatitis B virus in China. *Chin Med J* 2016;129:304–8.
- Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010;362:1090–101.
- Zhou J, Liu YY, Lian JS, et al. Efficacy and safety of tenofovir disoproxil treatment for chronic hepatitis B patients with genotypic resistance to other nucleoside analogues: a prospective study. *Chinese medical journal* 2017;130:914–9.